NIH Office of Dietary Supplements Panel Presentation Robert W. Henderson, P.D., Chairman of the Board Nutramax Laboratories, Inc. June 16, 2010

Nutramax Laboratories, Inc. was founded in 1992 and developed the first glucosamine and chondroitin sulfate combination product and is still the only glucosamine/chondroitin brand that has been the subject of peer-reviewed, published U.S. controlled clinical studies. We have sales domestically as well as internationally and Cosamin® is the number one glucosamine/chondroitin sulfate brand recommended by Orthopedic Specialists[1]. We are a privately held, Christian-based company located in Edgewood, MD with approximately 105,000 square feet of factory, laboratory, warehouse and office space. Our mission is to provide safe, effective, high quality nutritional health products that support the active lifestyles of people and animals. We seek to meet this objective through Research & Development of our products. Currently we maintain an intellectual property portfolio that includes numerous patents, many including claims related to dietary supplement ingredients. We have invested over $18 million in Manufacturing and Quality Compliance equipment to maintain what we believe are the highest standards practiced today in the dietary supplement industry. We currently have products supporting joint, heart, brain, liver, urinary tract, and digestive health. Marketing and sales of our products are largely handled by internal organizations, although we also have relationships with several national distributors and brokers.

At present we employ approximately 237 employees. Within these ranks we employ 11 individuals with doctorate level degrees, 19 employees with Master degrees and 52 employees with Bachelor degrees. Many of our employees have extensive experience in

the pharmaceutical industry, including about 35 positions in Quality Compliance and 76 employees in Manufacturing Operations (1 to 2 ratio).
Most of our product manufacturing is performed at our Edgewood, Maryland location in a Class 100,000 environmentally controlled facility. This production environment includes HEPA-filtered air, humidity controlled in a positive pressure "bubble" with air locks to prevent the ingress of contaminants. All of our manufacturing employees have extensive SOP training as well as cross training on multiple pieces of manufacturing equipment. In addition, all of our manufacturing employees are given routine Good Manufacturing Practice (GMP) training and safety training on an on-going basis throughout the year.

Quality is a State of Mind – an Ongoing Process of Improvement

Position on cGMP Regs

Nutramax Laboratories, Inc. supports strong current Good Manufacturing Practices (cGMPs) to ensure that dietary supplement products are not adulterated with contaminants or impurities, and are labeled accurately. As such we support and believe that we exceed the Dietary Supplement cGMPs issued by the FDA. By way of comparison the most significant differences between Dietary Supplement GMPs and Pharmaceutical GMPs are in the areas of Validation and Stability/Expiration Dating concepts. At Nutramax Laboratories, Inc., we basically follow the manufacturing standards practiced by the pharmaceutical industry. In February 2006, the FDA conducted a routine inspection of our manufacturing operations that yielded no 483's (form issued by FDA when they find problems), no deficiencies, and in the inspector's final report even acknowledged that we use "drug GMPs" in the manufacturing of our dietary supplements.

To further bolster our philosophy of quality, we are installing a paperless manufacturing system. In addition, Nutramax Laboratories, Inc. fully complies with the requirement for mandatory reporting of serious AERs for consumer dietary supplements that went into effect in December 2007. The effort required to comply with the new AER law was truly minimal since we already had a system in place prior to this requirement.

Evidence Based Studies

Nutramax Laboratories, Inc. is committed to sound science in the development of our products. Many of our studies are done independently (we typically only supply the intervention and/or placebo) by Universities as well as the US Department of Defense. We have numerous published studies on our products with many published in recognized journals including:

Osteoarthritis and Cartilage
Journal of Complementary and Integrative Medicine
Biopharmaceutics and Drug Disposition
Clinical Orthopedics and Related Research
Journal of Veterinary Pharmacology and Therapeutics
Journal of Biomedical and Material Research
Veterinary Journal
Archives of Internal Medicine
American Journal of Veterinary Research
Journal of Rheumatology
Military Medicine

Just in the last 24 months, we have presented twenty oral and poster presentations at various U.S. and International venues such as:

ICRS (International Cartilage Research Society)
OARSI (Osteoarthritis Research Society International)
ORS (Orthopedic Research Society)
World Biomaterials Congress in Amsterdam
Society for Biomaterials
American College of Veterinary Internal Medicine
American College of Veterinary Surgeons
Veterinary Orthopaedic Surgeons

To support scientific education, we have established a basic science research internship program that covers studies in both human and veterinary medicine. Over the last five years, we have trained twenty eight students, residents, and fellows through this program.

An extensive amount of work takes place before we officially initiate new product manufacturing. We begin with an in-depth literature search for safety and efficacy on the material we are considering. Our scientists evaluate the published literature before we proceed. Once we decide to proceed with initial development, we obtain sample material and determine if the supplier meets our commitment to manufacturing quality. If satisfied on these issues, our Quality Assurance department begins the supplier audit process.

Quality Assurance

Auditing Suppliers, Laboratories, and Contract Manufacturers

At Nutramax Laboratories, Inc., we have a fully staffed Quality Assurance (QA) department. On the QA team there is a Supplier Quality Engineer (SQE) who is responsible for coordinating both internal audits as well as external audits of our suppliers, labs and contract manufacturers that we use. Internally, the SQE will audit multiple times throughout the calendar year pursuant to 21 Code of Federal Regulations (CFR), Part 111, Dietary Supplement Good Manufacturing Practices.

In addition to the internal audits, we conduct routine periodic external audits of our distributors and suppliers of our active and inactive raw materials, laboratories as well as a few off-shore manufacturers licensed to make our products for overseas markets.

There are approximately 8 employees qualified to conduct these audits including the SQE. These individuals, including the SQE, have between 5-30 years experience in the pharmaceutical industry.

We are very proud of the priority and focus we give this part of the business. It is vital to our long term business interests that our ingredients meet our high standards of quality; that laboratories used in the testing of our products deliver validated results; and that production facilities used for our products practice sound GMPs to meet our customers' expectations for our products.

Analytical Chemistry

The goal of Analytical Chemistry (AC) is to develop assays for new products, validate the methods and transfer them to our QC lab once the assay development is completed. The goal of the QC lab is to take those developed, validated and transferred methods and run them routinely to test and release raw materials and final products used and manufactured or packaged.

The AC Lab is currently comprised of scientists that have either a Ph.D. in Analytical Chemistry, Masters Degrees, or Bachelors Degree in the science field.

The AC Lab is outfitted with state-of-the-art analytical instrumentation including several Gas Chromatograms (GCs), a GC-Mass Spectrophotometer (MS), Inductively Coupled Plasmospectroscopy (ICP), several High Liquid Performance Chromatography (HPLCs) and Ultra Liquid Performance Chromatography (UPLC) units. Other equipment on site includes centrifuges, a particle size analyzer (PSA), microbalances, balances, and pH meters.

The AC scientists are responsible for the development of methods and sample extraction techniques. Once the methods of sample prep and the assays are developed, these methods go through validation. The validation of the assays allows us to establish specification and ranges with the variability of the assay methodology included for each active in the raw and finished forms. Once methods are validated and specifications are established by the AC group, they are transferred to the QC lab. This is done under a formal protocol, using a scientist from the AC lab and an analyst in the QC lab.

Stability

In addition to assay development, validation and transfer, the AC lab performs a critical function to new product development in the area of stability. The AC lab has a stability program for marketed products including new products under development. The stability program runs protocols and studies in accordance with the International Conference on Harmonization (ICH) and FDA guidelines. Running these protocols at various temperatures and conditions (for example 25 degrees C/60% Relative Humidity(RH); 30 degrees C/65% RH and 40 degrees C/45% RH) helps us understand the long term stability and shelf life of our products. This is not a requirement in the dietary supplement industry, but a requirement for Nutramax Laboratories, Inc. to ensure the label claim of the products we manufacture throughout their life cycle.

Quality Control (QC)

QC tests products on stability for the stability group. They also test raw materials and final products before they are sold to the public. A few tests are sent out to qualified outside laboratories but more of these assays are being brought in house to keep the costs of finished products down, have more control and to improve turn around times.

As part of our continuous improvement initiatives, the QC lab has implemented a new Laboratory Information System (LIMS). The LIMS is a validated software system that will enable us to direct samples, users and instruments to their fullest capacity in order to manage laboratory workflow most efficiently.

In addition, Nutramax Laboratories, Inc. has commissioned a brand new Microbiology Lab through which several products are currently being tested. The Lab's new Rapid Micro system has been validated and so have the individual products that are being tested with this new system. This has improved overall testing control and our turn around times since we no longer have to rely on an outside laboratory for this function. In time, the remainder of our products will be validated to go through this system as well.

The QC lab has fully implemented an in house environmental monitoring (EM) program. Given the addition of the new Micro lab and interpreting our data trends over the past year, the lab has been able to establish action and alert levels for the manufacturing and testing areas as it relates to total viable counts. This system allows us to monitor the

environment in which our products are being manufactured every week to ensure its cleanliness and aide in detail cleaning.

A Total Organic Carbon (TOC) Analyzer has been added to the QC lab. This allows us to detect total organic carbon as found in residuals, cleaners, water or product that may remain in our equipment after product run and subsequent wash. This is a key piece of equipment in our cleaning validation program which is again pharmaceutical standards based.

The QC Lab is in the process of implementing the Near Infrared (NIR) technique in the identification of our active and inactive raw materials. This technique is based on establishing a fingerprint of the specific raw material and comparing the incoming material against it. It is highly sensitive and accurate and improves our turn around time for release of raw materials to manufacturing. Next year, we are looking to employ the technology of the NIR to test final products for identity and adulterants.

How Nutramax Laboratories, Inc. Utilizes Scientific Research for Evaluating and Developing Dietary Supplement Health Products

The first step in product development is pre-clinical screening using *in vitro* tissue cell-based models that allow for molecular level explorations. These models examine cellular response to the test agent (ie. future potential active ingredients) that could help predict response in the body. They also provide information on how the agent may work and their potential mode of action. The dose response obtained *in vitro* also provides direction to range of doses *in vivo.*

Research and Development

The Nutramax Laboratories, Inc. R&D Department is headed by Dr. Carmelita G. Frondoza. Dr. Frondoza received her Ph.D. in Immunology from the Johns Hopkins University (JHU) and served for 12 years as Johns Hopkins Orthopaedics Research Director of Arthritis Surgery prior to coming to Nutramax Laboratories, Inc. She continues to maintain a part time appointment as Associate Professor at Johns Hopkins University and an Adjunct Professorship at Mississippi State College of Veterinary Medicine. The R&D team is composed of Bioengineers, cell and molecular biologists.

The R&D manager, who reports to Dr. Frondoza, has a Master's degree in Bioengineering and is currently completing her Ph.D.

To evaluate which raw materials we select for our products we use consensus scientific methods. We test these and our finished products on tissue cell models that are the structural units of organs in the body. Examples are cells from cartilage, bone, tendon, ligament, synovium, immune system and liver. To visualize the cells and what they produce (i.e. cytokines, chemokines), we use microscopy, protein chemistry and immunoassays. We also measure what these tissue cells models are capable of producing (i.e. gene transcripts) using molecular biology techniques such as quantitative real time polymerase chain reaction. We analyze biomarkers that can help reveal mechanisms of action of the ingredients and finished products. Our overall goal is to determine safety and efficacy of the ingredients and finished products at the cellular and molecular level.

Then we are ready to begin clinical trials as applicable. Once on the market we continue not only to monitor suspected adverse events, but address any concerns by physicians. At times we even initiate and/or support trials. For example with Cosamin®DS:

- Since glucosamine is a glucose-like molecule, how does it effect glycemic control in patients with type 2 diabetes mellitus? This fear was alleviated by an independent study conducted by the Department of Rheumatology, 59th Medical Wing, Wilford Hall Medical Center, Lackland Airforce Base in Texas and the Department of Medicine, Uniformed Services University of the Health Sciences in Bethesda Maryland and published in the Archives of Internal Medicine[3].

- Another concern was whether chondroitin sulfate alters prothrombin time which was again looked at in another independent clinical study conducted by Medical Department, Naval Amphibious Base Little Creek, Norfolk, Virginia and published in Military Medicine[4].

Research Issues with Dietary Supplements

Often Dietary Supplement (DS) materials are more difficult to study than pure chemicals. DS studies may fail for the following reasons:

1. Poor design including outcome measures, population group, and improper dosing.
2. Not understanding how the material works at the molecular level.
3. The use of assay methods that are not fully validated for the product being studied.
4. Lack of bioavailability data.
5. Conflicts of interest of researchers due to receiving major grants and financial interest in competing pharmaceutical companies.
6. Inherent bias of some researchers against dietary supplements.

Two examples of our difficulties encountered with dietary supplement clinical studies:

1. First example: We had an IRB approved study underway and patient enrollment had begun. The study was discontinued because the investigators could not enroll enough patients for our study as they were given a large grant to study a drug in the same patient population. The investigators and research hospital involved were attracted by the larger funding and prestige of the pharmaceutical study and our study was placed on hold.
2. Second example: The design, conduct and communication of the results of the NIH funded $16 million Glucosamine/Chondroitin Sulfate Arthritis Intervention Trial (GAIT) for painful knee OA. Nutramax Laboratories, Inc. (as well as its chondroitin sulfate manufacturer) supplied the chondroitin sulfate material used in the study. It is commendable that the NIH took the initiative to fund a study to evaluate nutraceuticals and in particular, glucosamine/chondroitin sulfate for osteoarthritic knees. However, there were weaknesses in the design and conduct of the study. The study was performed by a number of experts who had potential conflicts of interest which were revealed in the NEJM[2] (page 807). Some of these experts when addressing the media diminished the findings addressed in post study publications showing: (i) the combination of glucosamine hydrochloride (HCl) and chondroitin sulfate was effective in moderate to severe OA patients with knee pain; and (ii) the lack of response in patients with mild pain may have been due to a floor effect, limiting the ability to detect response.
   The positive message that this supplement worked and allows for a safe option for patients with knee pain continued to get watered down when the study was presented at conferences.

With these kinds of obstacles to overcome, it is no wonder most of the dietary supplement companies would rather market to consumers with advertising than devote their resources to peer reviewed publishable clinical studies. With proper incentives and a level playing field, we believe more dietary supplement companies would devote the resources needed to conduct meaningful research.

We appreciate being invited to speak to such a distinguished crowd and would personally like to invite you to visit our facility which is located just north of Baltimore, MD. Just mention that you attended this practicum and contact:

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Thank you again!

References:

[1] Source: SLACK Incorporated Market Research Survey, April 2009. Survey conducted of Orthopedic Specialists relating to glucosamine/chondroitin sulfate brands.

[2] Clegg DO, et al. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. N Engl J Med. 2006; 354: 795-808.

[3] Scroggie, D.A., et al., The Effect of Glucosamine-Chondroitin Supplementation on Glycosylated Hemoglobin Levels in Patients with Type 2 Diabetes Mellitus. Arch of Int Med. 2003; 163: 1587-1590.

[4] Leffler CT, et al., Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. Mil Med. 1999 Feb;164(2):85-91.